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Excess cardiovascular mortality during the first year of the COVID-19 pandemic

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ABSTRACT. ***Introduction.*** Excess mortality is an objective indicator that allows assessing the impact of the pandemic on public health and identifying the features of the epidemiological process. We analyzed data on mortality associated with cardiovascular diseases (CVD) during the first year of the COVID-19 pandemic in 16 cities of the Russian Federation. ***The aim*** was to quantify excess mortality associated with CVD during the first year of the COVID-19 pandemic. ***Materials and methods.*** We used aggregated daily data on mortality from CVD during the first year of the COVID-19 pandemic (2020) and three to ten years preceding the start of the pandemic in 16 cities of the Russian Federation. For each city, time series of mortality data were generated with a time interval of 1 month, taking into account long-term and seasonal trends. To calculate expected mortality rate for every month of 2020, which would have been observed in the absence of the COVID-19 pandemic, adaptive models were used: exponential smoothing and autoregression and integrated moving average, allowing to take into account the trend, seasonality and cyclicality of the series and are presented in the form of expected mortality from CVD for each month of 2020 with 95% confidence intervals. Excess mortality during the first year of the pandemic is the cumulative number of excess deaths from CVD from April 1 to December 31, 2020. ***Results.*** A high level of excess mortality was identified in each of the cities studied. The average excess mortality rate from cardiovascular diseases was 17.7%. The cities where the highest values were recorded are Lipetsk (36.9%), Norilsk (34.9%), Omsk (32.6%). The lowest levels were noted in Irkutsk (6.1%), Petropavlovsk-Kamchatskiy (8.3%) and Arkhangelsk (10.0%). In Norilsk, Omsk, Magadan, Severodvinsk, Arkhangelsk, excess mortality from cardiovascular diseases among women was higher than among men. In Krasnoyarsk, and Yakutsk, the mortality rate among men, on the contrary, exceeded the rates among women. ***Conclusion.*** The COVID-19 pandemic had a significant impact on excess cardiovascular mortality, due to the peculiarities of the organization of the work of healthcare institutions, the introduction of strict restrictive measures, and a negative psycho-emotional background among the population of the Russian Federation. Taken together, these aspects may have caused changes in providing medical care, delayed visits of citizens to medical organizations, delayed diagnosis and, as a consequence, an increase in mortality from somatic diseases including CVD.

KEYWORDS: COVID-19 pandemic, mortality, excess mortality, cardiovascular diseases, epidemiology

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Избыточная смертность от болезней системы кровообращения в первый год пандемии COVID-19

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РЕЗЮМЕ. ***Введение.*** Избыточная смертность является показателем, позволяющим отобразить влияние пандемии на уровень смертности и выявить особенности эпидемиологического процесса. ***Цель*** — проанализировать избыточную смертность от болезней системы кровообращения (БСК) в 16 городах в первый год пандемии новой коронавирусной инфекции (COVID-19). ***Материалы и методы.*** Использованы агрегированные ежедневные данные о смертности от БСК в течение первого года пандемии COVID-19 (2020) и 3–10 лет, предшествующих началу пандемии, в 16 городах Российской Федерации. Для каждого из городов сформированы временные ряды данных по смертности с временным интервалом в 1 месяц с учетом долгосрочного и сезонного трендов. Для прогнозирования ожидаемого уровня смертности в каждый месяц 2020 года использовались адаптивные модели экспоненциального сглаживания и авторегрессионные проинтегрированные модели скользящего среднего. Избыточную смертность в течение первого года пандемии считали как кумулятивное число избыточных смертей от болезней системы кровообращения с 1 апреля по 31 декабря 2020 года по сравнению с ожидаемыми значениями. ***Результаты.*** Средний уровень избыточной смертности от БСК составил 17,7%. Города, где зафиксированы самые высокие значения, — Липецк (36,9%), Норильск (34,9%), Омск (32,6%). Самый низкий уровень отмечался в Иркутске (6,1%), Петропавловске-Камчатском (8,3%) и Архангельске (10,0%). В Норильске, Омске, Магадане, Архангельске и Северодвинске уровень избыточной смертности от БСК среди женщин был выше, чем среди мужчин. В Красноярске и Якутске смертность среди мужчин, напротив, была выше. ***Выводы.*** Выявлена существенная избыточная смертность от БСК во всех изучаемых городах, что может, как минимум, частично объясняться особенностями организации работы учреждений здравоохранения в период пандемии, введением строгих ограничительных мероприятий, страхом населения перед обращением за медицинской помощью из-за угрозы инфицирования. В совокупности данные аспекты предположительно привели к изменению порядка оказания медицинской помощи, отсроченному обращению граждан в медицинские организации, более поздней диагностике и, как следствие, к росту уровня смертности от соматических заболеваний, включая БСК.

КЛЮЧЕВЫЕ СЛОВА: пандемия COVID-19, смертность, избыточная смертность, болезни системы кровообращения, эпидемиология

INTRODUCTION

On March 11, 2020, the World Health Organization named the new coronavirus infection a pandemic due to the rapid spread of the disease and high mortality rates [1]. The causative agent of new coronavirus infection is coronavirus-2, which causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronovirus-2 belongs to the subgenus Sarbecovirus of the genus *Betacoronavirus*, subfamily *Orthocoronavirinae*, family *Coronaviridae*. The virion is pleomorphic, its genome is represented by non-segmented single-stranded RNA. The structure of the viral particle is represented by proteins: spike protein (S-protein), envelope (E-protein), membrane (M-protein), nucleocapsid (N-protein). S-protein plays the leading role in the development of the disease. This protein facilitates adhesion and penetration of the virion into the target cell. N-protein is responsible for morphogenesis of the viral life cycle into the human body. Inside the target cell, virion depresses gene expression of the cell, including interfering with the activation of the adaptive humoral component of the immune system, inhibiting the production of interferons. Viral proteins are synthetized using endoplasmic reticulum of the host cell. Virions exit from the cell by exocytosis throw lysosomes, formed in the Golgi complex [2].

Despite the predominant damage to the epithelial cells of the respiratory tract, SARS-CoV-2 is tropic to tissues of other body systems. Surface S-protein connects with angiotensin converting enzyme 2 (ACE2) initiating proteolytic changes in the host-cell's membrane. This promotes its introduction inside by endocytosis or by direct fusion [2]. SARS-CoV-2 uses transmembrane protease, serine 2 (TMPRSS-2), cathepsin L as receptors, penetrating into pneumocytes, enterocytes, endothelial cells, myocytes, neurons and other cells [3]. Thus, when a virus penetrates a cell, its vital processes are disrupted, the virus actively replicates, and other cells become infected. Hypercytokinemia plays an important role in the pathogenesis of the disease: under the influence of hypoxia, increased production of cytokines and hypercatecholaminemia, the synthesis of active forms of oxygen increases. It leads to the development of oxidative stress and tissue damage. Cytokines and active forms of oxygen influence the host-cells promoting the destruction of intercellular contacts and filling the interstitial space of parenchymal organs with fluid. Due to the intense inflammatory response, tissue infiltration by immune cells occurs, which disrupts microcirculation and contributes to their damage [4]. Tissues affected by SARS-CoV-2 lost the normal function, what is very dangerous for patients with comorbid pathology. The course of existing chronic diseases worsens or complications associated with COVID-19 develop. The connection between COVID-19 and the development of circulatory system diseases (CVDs) is most often described [5].

The most common diseases of the circulatory system in the structure of morbidity and mortality include ischemic heart disease (ICD-10 code I20–I25) and cerebrovascular diseases (ICD-10 code I60–I69). According to Rosstat, in 2018, ischemic heart disease accounted for 28.4% of total mortality [6]. In 2019, 8.9 million deaths were occurred because of this disease accounting 16% of the total lethal outcomes in the world [7]. High rates of excess mortality in patients with coronary heart disease have been recorded with the onset of spread of the disease [6, 7]. Damage of the myocardium in patients with COVID-19 infection can be realised in different ways including direct damage to cardiomyocytes by the SARS-CoV-2 virus, development of a cytokine storm, endothelial dysfunction, hypercoagulation, hypoxemia and respiratory failure. Inflammation process can initiate atherosclerotic plaque rupture or coronary thrombosis. In patients with chronic coronary stenosis, there is also an imbalance between oxygen delivery to cardiomyocytes and their metabolic needs, which aggravates damage to cardiac tissue [8]

A possible link between COVID-19 and stroke risk has also attracted the attention of researchers. Ischemic strokes during the pandemic were more severe and more often fatal [9].

Official statistical data did not allow for an objective assessment of COVID-19 mortality in the population due to differences in coding and death registration approaches. This was caused by the low availability of SARS-CoV-2 testing early in the pandemic, alongside concurrent changes in mortality rates from other causes. In the Russian Federation, COVID-19 could be listed on a death certificate in two cases: when SARS-CoV-2 infection was identified as the underlying cause of death or as another significant condition contributing to death [10]. Due to the lack of clear separation between the principles for determining COVID-19 as the primary cause of death and deaths associated with COVID-19, there were discrepancies in how the underlying cause of death was established, leading to variations in statistical data. Postmortem COVID-19 testing was permitted, with the requirement that examinations of deceased individuals suspected of having COVID-19 include a detailed description of morphological changes in the respiratory system. However, in some regions, both antemortem and postmortem COVID-19 testing were unavailable, which affected official statistics [11]. The most objective way to assess the quantitative impact of the COVID-19 pandemic on overall mortality is by calculating excess deaths.

Excess mortality is defined as the proportion of additional deaths to the predicted mortality rate for a given period of time. Forecasting is made using mortality data for the period preceding the pandemic [12].

The COVID-19 pandemic impacted excess mortality not only directly linked to COVID-19 but also due to other causes, influenced by factors such as changes in healthcare system operations, strict restrictive measures, and the negative psychological and emotional state among the Russian population. According to Rosstat (Russian Federal State Statistics Service), in 2018, there were 79.9 hospital beds per 10,000 people [13]. However, with the sharp rise in cases during the pandemic, the demand for medical care surged. As a result, many hospitals or departments were repurposed to treat infectious disease patients, increasing the number of available beds. While these reorganization measures were necessary to assist COVID-19 patients, they simultaneously reduced access to medical care for patients with other conditions. Additionally, many individuals avoided seeking medical help due to fears of contracting COVID-19 in healthcare facilities [14].

AIM

To analyze excess mortality from cardiovascular diseases (CVD) during the first year of the COVID-19 pandemic in 16 cities of the Russian Federation, belonging to 5 different Federal Districts (FDs).

MATERIALS AND METHODS

Data collection. In this study we used aggregated daily data on mortality from CVD during the first year of the COVID-19 pandemic (2020) and 3–10 years preceding the onset of the pandemic in 16 cities in Russia. Five cities of the Russian Federation were included in the study: Northwestern Federal District (Arkhangelsk, Murmansk, Severodvinsk, Syktyvkar), Siberian Federal District (Angarsk, Bratsk, Irkutsk, Omsk, Norilsk, Krasnoyarsk), Far Eastern Federal District (Khabarovsk, Magadan, Petropavlovsk-Kamchatsky, Yakutsk), Central Federal District (Lipetsk), Southern Federal District (Astrakhan).

Forecasting the expected mortality rate. The analysis utilized aggregated daily mortality data from the first year of the COVID-19 pandemic (2020) and the 3–10 years preceding it, stratified by sex and age groups (18–44, 45–59, ≥60 years). For each city, time series mortality datasets were constructed with a monthly interval, accounting for long-term and seasonal trends. To eliminate irregular components (noise) in the series, values deviating from the mean by more than two standard deviations (outliers) were replaced with values corresponding to the mean ± two standard deviations.

To forecast the expected mortality rate in 2020 — the level that would have been observed in the absence of the COVID-19 pandemic — adaptive modelling techniques were employed: exponential smoothing and autoregressive integrated moving average (ARIMA). These methods account for trends, seasonality, and cyclical patterns in the data. A detailed description of these models Is provided by the authors in a publication dedicated to excess mortality estimation methods during the COVID-19 pandemic [12]. Each time series served as the dependent variable for predictive modelling. The optimal forecasting model was selected based on the following criteria: highest stationary coefficient of determination (R-squared), lowest root mean square error (RMSE), lowest mean absolute percentage error (MAPE), lowest normalized Bayesian information criterion (BIC) value, statistical significance level in the Ljung–Box test.

Since most time series exhibited seasonality but lacked a trend, the simple seasonal exponential smoothing model was most frequently used (74.9%) for forecasting expected mortality values. The additive Winters' exponential smoothing model was applied to 23.5% of the time series, while the ARIMA (0,0,0) model was used for the remaining 1.6%. Using these models, we calculated the expected number of CVD deaths for each month of 2020 in all 16 cities, along with their 95% confidence intervals (CIs).

Excess mortality estimation. Excess mortality was calculated as the difference between the observed number of deaths each month in 2020 and the predicted mean number of deaths derived from time series analysis of mortality statistics spanning several pre-pandemic years. The number of years with available daily data for analysis ranged from 3 (Murmansk) to 10 (Arkhangelsk, Severodvinsk, etc.). Cumulative excess CVD mortality during the first pandemic year was computed as the sum of excess CVD deaths from April 1 to December 31, 2020.

RESULTS

The highest level of excess mortality from CVD was observed in the cities of the Siberian (on average 31.9%), Central (27.9%), Southern (26.3%) federal districts, and the lowest — in the Northwestern (23.56%), Far Eastern (20.6%) and Volga (14.6%) federal districts. No clear geographic patterns along the north-south, west-east axes in excess mortality from CVD were identified.

On average, in the first year of the pandemic, the number of deaths from CVD in the studied cities increased by 17.7%, taking into account seasonal and long-term trends. The maximum value of excess mortality from CVD was recorded in Lipetsk (36.9%), and the minimum in Irkutsk (6.1%). Detailed information on excess mortality from CVD in the cities studied in the first year of the pandemic is presented in Figure 1.

Pronounced gender differences were observed in excess mortality rates in the cities. In Norilsk, Omsk, Magadan, Arkhangelsk, Severodvinsk, excess mortality rates from CVD among women

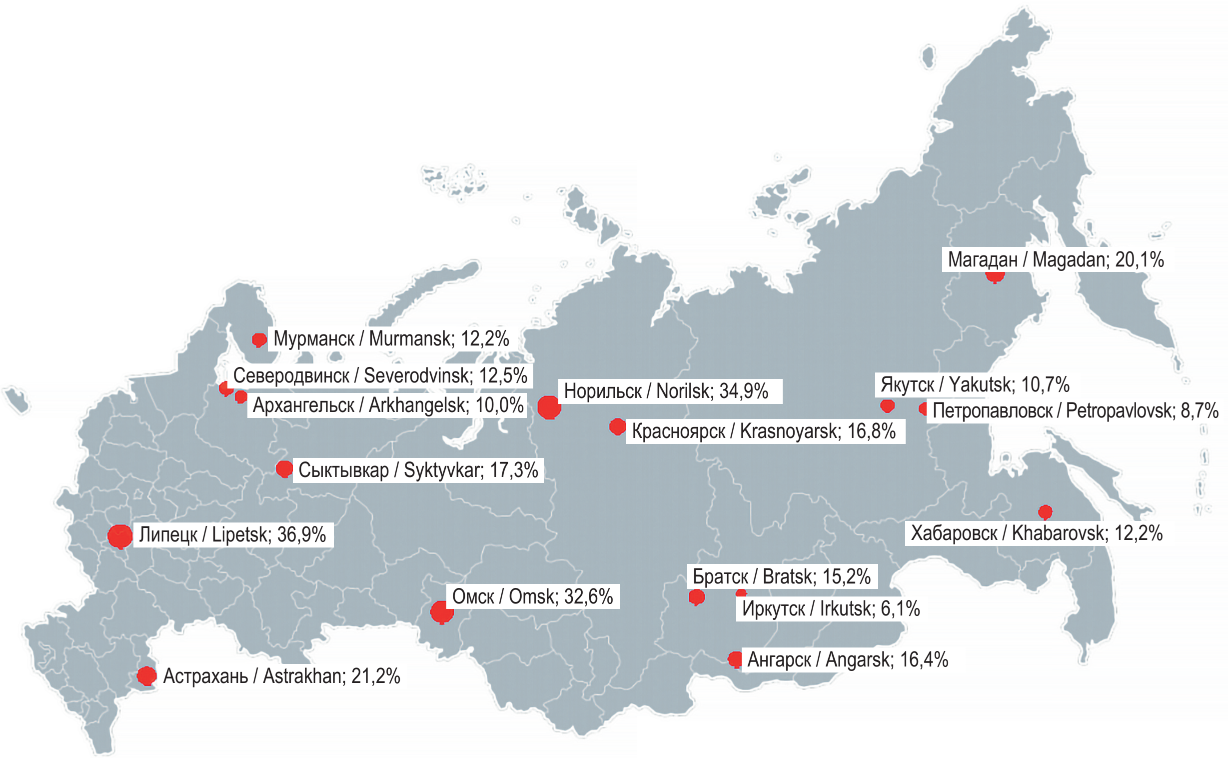

Fig. 1. Map of excess cardiovascular mortality in 16 Russian towns in 2020

Рис. 1. Картограмма избыточной смертности от болезней системы кровообращения в 16 городах Российской Федерации в 2020 году

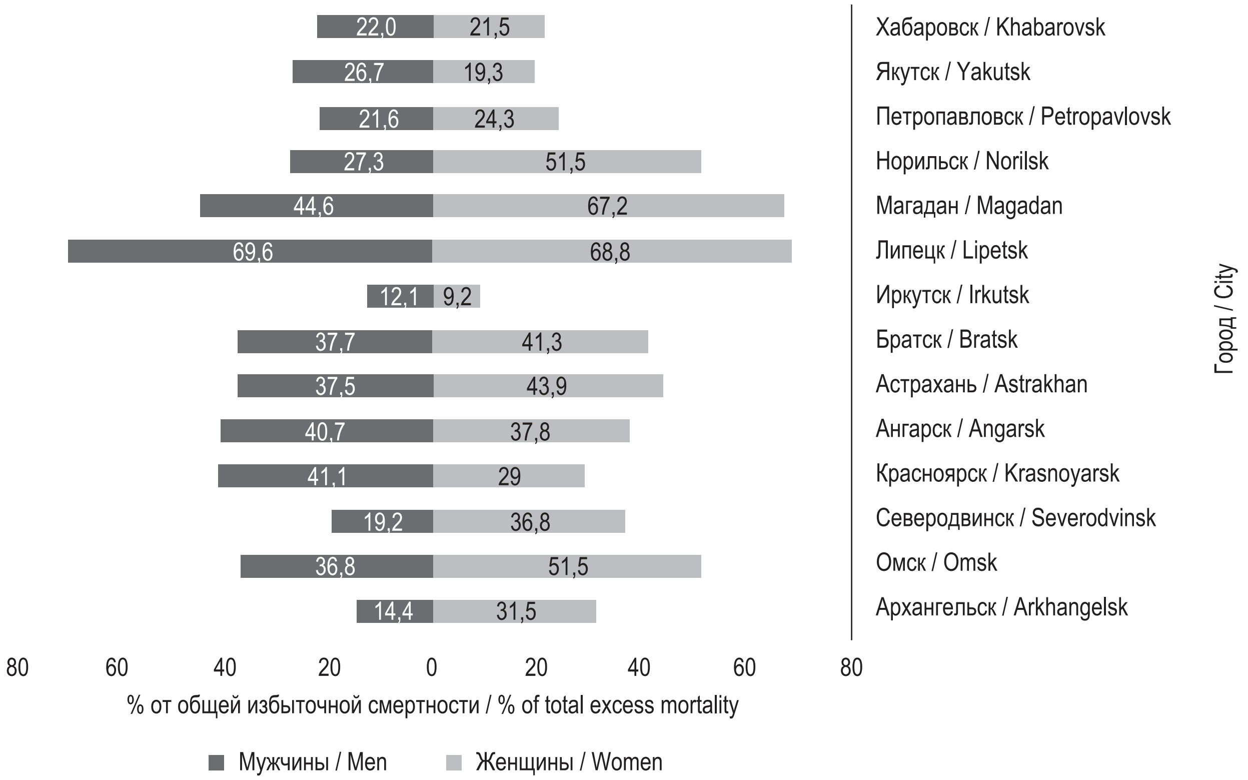

Fig. 2. Proportion of cardiovascular deaths in excess of all-cause mortality in 16 Russian towns in 2020 across genders

Рис. 2. Доля смертей от болезней системы кровообращения в структуре избыточной смертности от всех причин в 16 городах Российской Федерации в 2020 году по полу

were higher. In Krasnodar and Yakutsk, mortality was higher in men. In Khabarovsk, Petropavlovsk, Lipetsk, Irkutsk, Astrakhan and Angarsk there were no differences in mortality rates between men and women (Fig. 2)

DISCUSSION

In all 16 cities, we found that the number of deaths from CVD was higher than expected, in some cities by more than a third, regardless of long-term and seasonal trends, which raises the need to study the mechanisms that can explain the findings.

The key pathophysiological effects of SARS-CoV-2 include the increased production of pro-inflammatory cytokines such as interleukin-6, interleukin-2R, and tumor necrosis factor-α. This cytokine storm leads to increased vascular permeability, suppression of the immune system's anti-inflammatory defence mechanisms, and disruption of hemostasis. These pathological processes ultimately result in endothelial cell damage and the development of a hypercoagulation, which contributes to the onset of cardiovascular complications [11]. For cellular entry, the virion utilizes its S-protein to bind to ACE-2 receptors, a process that requires mediation by transmembrane proteases including TMPRSS-2 [15].

The pathogenesis of acute cardiovascular conditions involves a systemic inflammatory response and multiple organ dysfunction syndrome, which can exacerbate pre-existing chronic non-communicable diseases such as hypertension and diabetes mellitus. Acute decompensation of these conditions frequently leads to severe complications that may result in fatal outcomes [16]. In patients with COVID-19, strokes were observed to occur more frequently in individuals with chronic comorbidities not limited to cardiovascular pathology. The pathogenesis of COVID-19-associated strokes is primarily driven by hemostatic system disturbances characterized by increased procoagulant activity and decreased fibrinolytic capacity. These coagulation abnormalities stem from excessive production of proinflammatory cytokines that significantly worsen endothelial dysfunction [17].

Clinical studies, conducted during the pandemics before COVID-19, confirm a close relationship between viral respiratory infections and coronary heart disease, which is due to the direct effect of viruses on the myocardium. In some cases, symptoms of the infection could be disguised as acute coronary syndrome, which could lead to diagnostic errors, delayed initiation of etiological therapy and contributed to an increase in mortality [18].

COVID-19 pandemic significantly influenced mortality level of the population in Russia. Differences in statistical data between the cities and regions indicate the polymorphism of factors influencing population mortality [15].

Differences in the level of excess mortality by Federal Districts, regions and cities of the Russian Federation during the COVID-19 pandemic can presumably be explained by the characteristics of population density, age and gender characteristics in the population, the specifics of the economic structure of cities and other factors [19]. However, in our work, there is no clear pattern of differences in excess mortality either by geographic location, or by population size, or by income level.

In similar studies, based on secondary data, there is always a certain percentage of incorrectly coded postmortem diagnoses, which affects both the overall mortality statistics and the level of excess mortality. The coding of COVID-19-related deaths presents specific challenges in determining the underlying cause of death. According to established guidelines, COVID-19 was recorded as the underlying cause of death when fatal complications directly attributable to the infection (such as acute respiratory distress syndrome (ARDS), sepsis) were identified [20]. However, in cases where SARS-CoV-2 testing was not performed, and consequently no COVID-19 diagnosis was established, other conditions including CVD could be listed as the primary cause. This coding practice may have led to an overestimation of excess CVD mortality during the pandemic, particularly among the population above working age.

A special feature of determining the true mortality rate during the pandemic by monitoring excess mortality is that it takes into account the increase in mortality from causes not related to COVID-19 or its complications. The unpreparedness of the healthcare system for the mass admission of infectious patients forced the repurposing of hospital departments and beds, reducing the quantity and quality of routine medical care. Restrictive measures, increased anxiety, and fear of contracting a new disease reduced the level of population seeking medical care, including emergency care, which led to late diagnosis of a number of emergency conditions and affected the overall mortality rate. Due to the reduction in the volume of routine care, the number of screening activities was also limited, which negatively affected the diagnosis of a number of chronic diseases [21].

Authors of such studies note the role of excess CVD mortality, identifying this category as the primary contributor to increased deaths during the pandemic. In compared studies, demographic state statistics information databases were used as materials and methods. In this study, the database was constructed using daily aggregated mortality data during the first year of the COVID-19 pandemic (2020) and 3–10 years preceding the pandemic. This, in similar studies, some differences in the structure of excess mortality from CVD may be observed. In compared studies, the main causes of excess mortality from CVD during the COVID-19 pandemic are the specific features of the health care organisation; in this study, a large role is given to the specific features of coding the causes of death [22–24].

In foreign publications on excess mortality from CVD during the first year of COVID-19 pandemic, there was an increase in the mortality rate higher than expected. Statistical data is mainly presented by European countries, the USA in comparison with the situation in China. Researches indicate that COVID-19-related deaths can occur either during the acute phase of the disease due to the pathophysiological mechanisms of SARS-CoV-2's impact on the body's target cells, or as a delayed outcome among convalescent patients. After an infection, the risk of developing acute cardiovascular conditions increases. It is associated with the peculiarities of the pathogenesis of the infectious process and the risk of thrombosis. Differences in the time and intensity of the increase in excess mortality were revealed. In the studied sources, the increase in values is not uniform, which may be due to the peculiarities of the spread of infection in different territories, the specifics of the restrictive measures taken, the organization of medical care and the coding of fatal cases [25, 26].

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ADDITIONAL INFORMATION

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